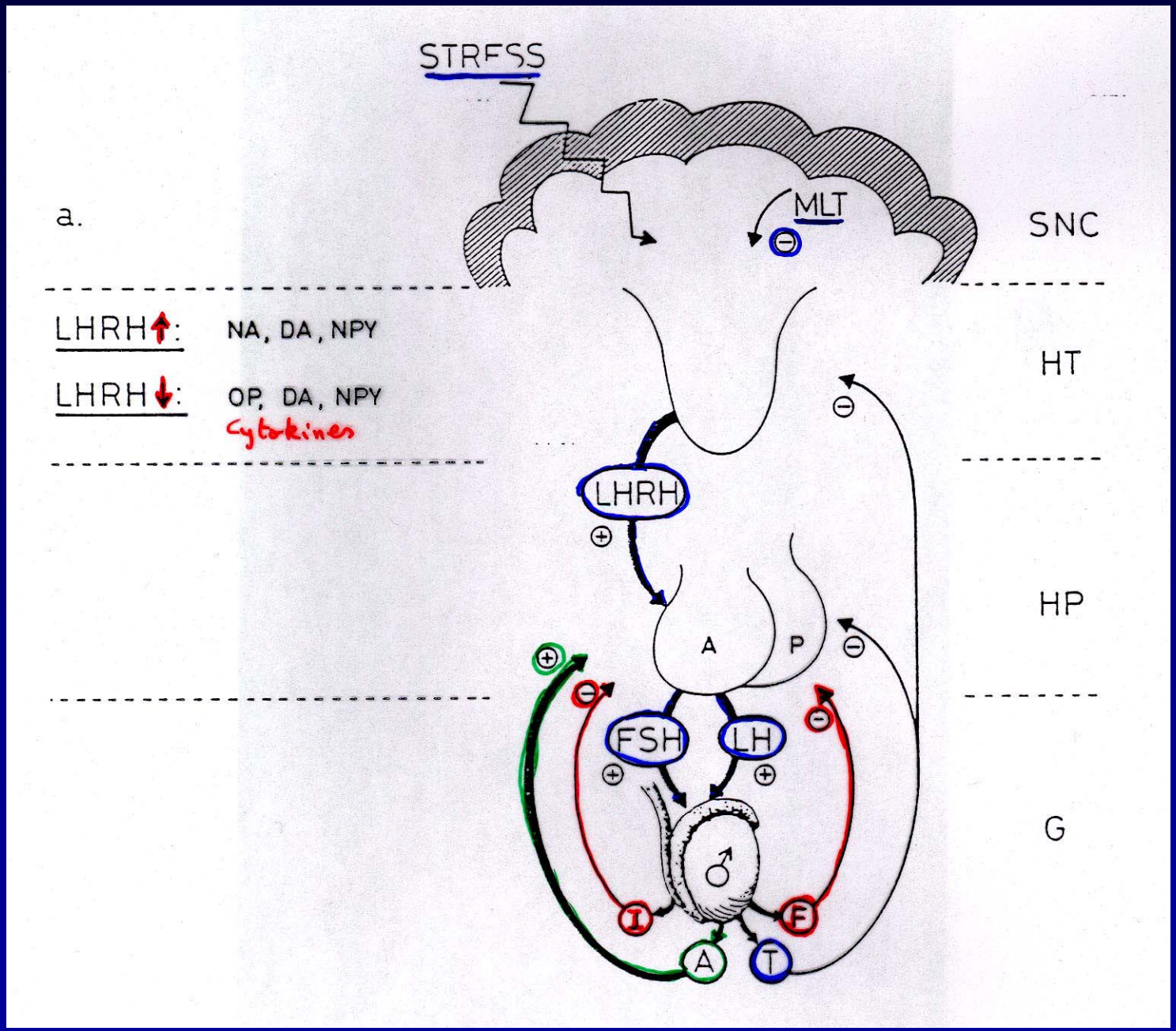
# HYPOTHALAMO – PITUITARY – GONADAL AXIS

- Physiology of the HPG axis
- Endogenous opioids and the HPG axis (exercise-induced menstrual disturbances)
- Effects of the immune system on the HPG axis (cytokines: interleukins and tumor necrosis factor)
- Hypogonadotrophic hypogonadism : hyperprolactinemia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SNC
LHRH↑: NA, DA, NPY
LHRH↓: OP, DA, NPY
Cytokines
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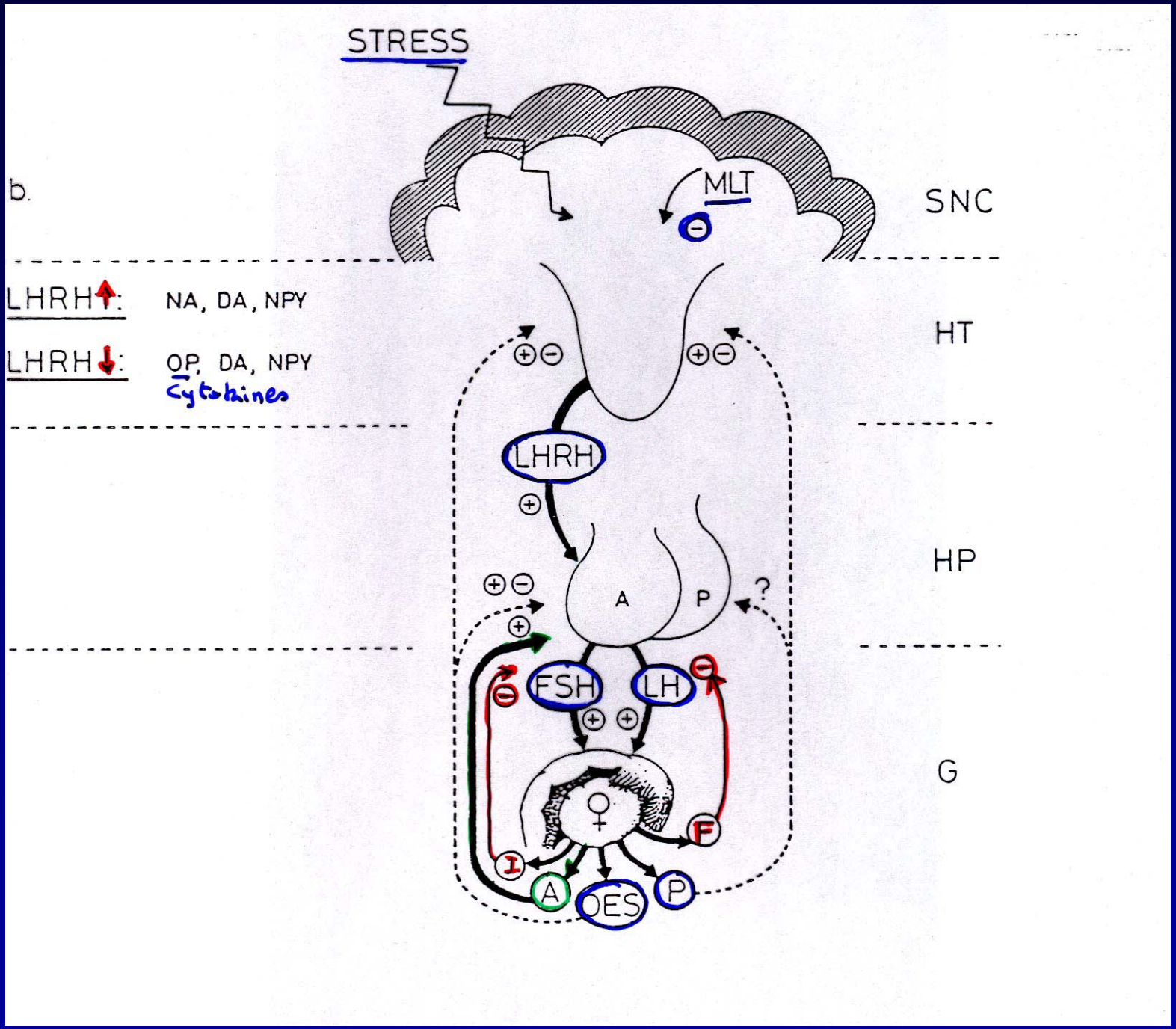
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## HYPOTHALAMUS

**LHRH : decapeptide**

**(pattern of administration crucial for pituitary response : pulsatile vs continuous administration)**

## PITUITARY

**LH, FSH : glycoproteins composed of 2 chains : $\alpha$, $\beta$**

**$\alpha$ chains are identical**
**$\beta$ chains are specific for each hormone**
**$\beta$ chains are biological active**

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# GONADS

**Sex steroids**

- Estrogens
- Progestins
- Androgens

**Gonadal protein hormones**

- inhibins -
- activins + modulating FSH
- Follistatins -

# ENDOGENOUS OPIOIDS AND MENSTRUAL CYCLE DISTURBANCES

# CONCLUSIONS

- Exercise training frequently induces anovulatory menstrual cycles due to an increase in endogenous opioids
- Exercise-induced amenorrhoea increases the risk of long-term osteoporosis, and may reflect overtraining
- A decrease in percentage body fat inhibits GnRH through LEPTIN

# ENDOGENOUS OPIOIDS DURING PREGNANCY

# CYTOKINES : Polypeptides produced by cells from the immune system (macrophages, monocytes, lymphocytes)

- interleukins
- Tumor necrosis factor $\alpha$
- Interferon

- Cytokines are not only produced within the immune cells but also within :
  - Brain (astrocytes, glial cells, neurones (?)
  - Hypothalamus
  - Pituitary gland
  - Adrenal gland
  - Gonads
  - Thyroid gland

# PATHOLOGIES OF THE PITUITARY AND HYPOGONADISM

# PITUITARY ADENOMAS

| | |
|---|---|
| - Prolactinomas (PRL) | ~ 50 % |
| - Growth hormone (Acromegaly) | ~ 20 % |
| - ACTH (Cushing) | ~ 10 % |
| - TSH, LH-FSH, Alpha-subunit | rare |
| - Non functional tumors | ~ 15-20 % |

# PITUITARY ADENOMAS

- Endocrine effects : hyperfunction
  hypofunction
  both combined

- Mass effect : compression of surrounding structures (neurological, pituitary)

# SYMPTOMS OF MASS EFFECTS

- Headache

- Visual field defects : - superior temporal quadranopsia
  - bitemporal hemianopsia

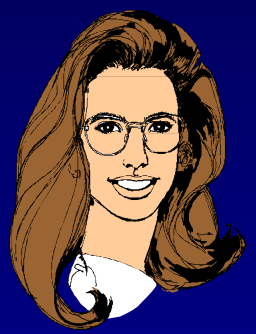
- Ophtalmology : lateral extension of adenomas into the cavernous sinus compromising function of III, IV and VI cranial nerve → diplopia

- Rinorrhea

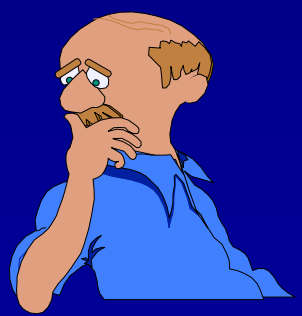
- Pituitary insufficiency

# PROLACTINOMA

**The most frequent pituitary adenoma : ~ 50 %**



**: microadenoma (<10 mm) : 50 %**



**: macroadenoma (>10 mm) : more frequent**

# CLINICAL FEATURES IN WOMEN

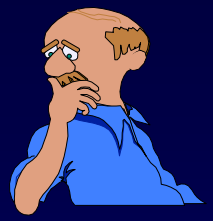
The classical manifestations of PRL excess :

- amenorrhea and galactorrhea

The gonadal dysfunction can produce any menstrual cycle dysfunction (amenorrhea, oligomenorrhea with anovulation, infertility)

Estrogen deficiency may result in

- decreased vaginal lubrification
- decreased libido
- osteopenia



# CLINICAL FEATURES IN MEN

Galactorrhea is significantly less frequent than in women

Hypogonadism is responsible :

- decreased libido
- impotence
- infertility
- loss of axillary, facial, chest and pubic hair
- slight testicular atrophy
- gynecomasty

# DOES HYPERPROLACTINEMIA ALWAYS MEAN THE PRESENCE OF A PROLACTINOMA?

# CAUSES OF HYPERPROLACTINAEMIA (I)

- Physiological
- Pharmacological
- Pathological
- Idiopathic
- Other causes

# CAUSES OF HYPERPROLACTINAEMIA (II)

**Physiological**

Pregnancy

Nursing

Nipple stimulation

Stress (physical, psychological, hypoglycemia)

Exercice

Food intake

Sleep

# CONDITIONS FOR BLOOD SAMPLING IN CASE OF SUSPECTED HYPERPROLACTINAEMIA

Blood sampling :

- in a fasting state
- between 8h and 12h
- take 2 - 3 blood samples at 30 min intervals (stress)

# CAUSES OF HYPERPROLACTINAEMIA (III)

**Pharmacological**

**Numerous drugs stimule PRL**

***Antihypertensive drugs :***

**- reserpine, a-methyldopa, verapamil**

***Neuroleptics & antidepressants :***

**- phenothiazines, butyrophenones, IMAO, benzamide, imipramine...**

# CAUSES OF HYPERPROLACTINAEMIA (IV)

**Pharmacological**

***Antiemetics :*** **metoclopramide, domperidone**

***Hormones :*** **estrogens (high dosage), TRH**

***Opiates***

***Anti-histaminic :*** **cimetidine**

***Anti-tbc :*** **isoniazide**

# CAUSES OF HYPERPROLACTINAEMIA (V)

## Pathological

- **Prolactinomas**
- **Mixed pituitary adenomas : GH + PRL**
- ***Defective hypothalamic dopamine secretion or transport to the lactotroph* :**
  - **Hypothalamic tumors**
  - **Pituitary tumors (pseudoprolactinoma)**
  - **Trauma (stalk section)**
  - **Radiotherapy sequellae**

# CAUSES OF HYPERPROLACTINAEMIA (VI)

- *Stimulation of the lactotroph :*
  - **hypothyroidism (TRH)**
- *Other causes :*
  - **renal failure**
  - **liver cirrhosis**
  - **diseases of the chest wall**
  - **PCOS**
- *Macroprolactinaemia (Big - Big PRL)*

# INVESTIGATIONS OF HYPERPROLACTINAEMIA

When a hyperprolactinaemia is suspected, before further and expensive investigations are proposed, it is necessary to

- Obtain a careful history of drug intake
- Eliminate a primary hypothyroidism
- Control kidney and liver functions
- In women with recent onset of amenorrhea or galactorrhea : pregnancy test

# DIAGNOSIS OF HYPERPROLACTINAEMIA

Basal PRL levels

- Values >400 ng/ml are virtually diagnostic of prolactinoma
- Values between 100 and 300 ng/ml are usually caused by a prolactinoma which is radiological evident
- If PRL values < 100 ng/ml : can be difficult !
- There is generally a good correlation between PRL levels and the size of the adenoma

# TRH TEST FOR PRL

- 200 μg TRH i.v.
- Normal response : increase of PRL by > 100 %
- Prolactinoma : no increase, or less than 30 % (macro) and less than 51 % (micro)
- But does not exclude all forms of functional hyperprolactinaemia

# INVESTIGATIONS OF PROLACTINOMAS

- Basal PRL levels
- TRH stimulation test on PRL (if doubts)
- In case of macroadenoma : test other anterior pituitary functions
- Imaging
- Visual field